Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1644PNH

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 28	Oct 21	EVENTLINE has been reloaded
NEWS 29	Oct 24	BEILSTEIN adds new search fields
NEWS 30	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 31	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 32	Nov 18	DKILIT has been renamed APOLLIT
NEWS 33	Nov 25	More calculated properties added to REGISTRY
NEWS 34	Dec 02	TIBKAT will be removed from STN
NEWS 35	Dec 04	CSA files on STN
NEWS 36	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 37	Dec 17	TOXCENTER enhanced with additional content
NEWS 38	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 39	Dec 30	ISMEC no longer available

NEWS EXPRESS	December 31 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information

```
 NEWS LOGIN     Welcome Banner and News Items
 NEWS PHONE     Direct Dial and Telecommunication Network Access to STN
 NEWS WWW       CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 15:15:50 ON 02 JAN 2003

=> file medline embase biosis scisearch caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'MEDLINE' ENTERED AT 15:16:03 ON 02 JAN 2003

FILE 'EMBASE' ENTERED AT 15:16:03 ON 02 JAN 2003
COPYRIGHT (C) 2003 Elsevier Science B.V.  All rights reserved.

FILE 'BIOSIS' ENTERED AT 15:16:03 ON 02 JAN 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'SCISEARCH' ENTERED AT 15:16:03 ON 02 JAN 2003
COPYRIGHT (C) 2003 Institute for Scientific Information (ISI) (R)

FILE 'CAPLUS' ENTERED AT 15:16:03 ON 02 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> s treatment
L1     7041944 TREATMENT

=> s l1 and neurological disorder
L2        4675 L1 AND NEUROLOGICAL DISORDER

=> s l2 and stroke
L3         645 L2 AND STROKE

=> s l3 and Jun kinase binding protein'
MISMATCHED QUOTE 'PROTEIN''
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
off or masking.

=> s l3 and JNK
L4           1 L3 AND JNK

=> d l4 cbib abs

L4   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
2002:522537   Document No. 137:88469  Treating neurological
     disorders using human apoptosis inhibiting protein.  Miller, Carol
     A.; Dong, Zhao Hui; Zhang-klompus, Yan (USA).  U.S. Pat. Appl. Publ. US
     2002090696 A1 20020711, 30 pp., Cont. of U.S. Ser. No. 419,694.
```

(English). CODEN: USXXCO. APPLICATION: US 2001-966561 20010927. PRIORITY: US 1998-PV111502 19981208; US 1999-419694 19991014.

AB The invention relates to methods of using full length amino acid sequence and cDNA sequence of protein human **JNK** interacting protein (hJIP-1) islet brain 1 (IB1) to treat **neurol. disorders** in human subjects. In an in vitro model of the apoptosis pathway, hJIP-1/IB1 inhibits phosphorylation of the transcription factor c-Jun in a dose-dependent manner. The invention includes antibodies that specifically bind to hJIP-1/IB1.

=> s JNK3
L5 384 JNK3

=> s l5 and JIP1
L6 1 L5 AND JIP1

=> d l6 cbib abs

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS

2002:522537 Document No. 137:88469 Treating neurological disorders using human apoptosis inhibiting protein. Miller, Carol A.; Dong, Zhao Hui; Zhang-klompus, Yan (USA). U.S. Pat. Appl. Publ. US 2002090696 A1 20020711, 30 pp., Cont. of U.S. Ser. No. 419,694. (English). CODEN: USXXCO. APPLICATION: US 2001-966561 20010927. PRIORITY: US 1998-PV111502 19981208; US 1999-419694 19991014.

AB The invention relates to methods of using full length amino acid sequence and cDNA sequence of protein human JNK interacting protein (hJIP-1) islet brain 1 (IB1) to treat neurol. disorders in human subjects. In an in vitro model of the apoptosis pathway, hJIP-1/IB1 inhibits phosphorylation of the transcription factor c-Jun in a dose-dependent manner. The invention includes antibodies that specifically bind to hJIP-1/IB1.

=> s l5 and IB1
L7 3 L5 AND IB1

=> dup remove l7
PROCESSING COMPLETED FOR L7
L8 3 DUP REMOVE L7 (0 DUPLICATES REMOVED)

=> d l8 1-3 cbib abs

L8 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS

2002:522537 Document No. 137:88469 Treating neurological disorders using human apoptosis inhibiting protein. Miller, Carol A.; Dong, Zhao Hui; Zhang-klompus, Yan (USA). U.S. Pat. Appl. Publ. US 2002090696 A1 20020711, 30 pp., Cont. of U.S. Ser. No. 419,694. (English). CODEN: USXXCO. APPLICATION: US 2001-966561 20010927. PRIORITY: US 1998-PV111502 19981208; US 1999-419694 19991014.

AB The invention relates to methods of using full length amino acid sequence and cDNA sequence of protein human JNK interacting protein (hJIP-1) islet brain 1 (**IB1**) to treat neurol. disorders in human subjects. In an in vitro model of the apoptosis pathway, hJIP-1/**IB1** inhibits phosphorylation of the transcription factor c-Jun in a dose-dependent manner. The invention includes antibodies that specifically bind to hJIP-1/**IB1**.

L8 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

2001:76431 Document No.: PREV200100076431. Human JIP-1/**iB1** is a phosphoprotein and inhibits JNK-mediated neuronal cell death. Dong, Z. (1); Miller, C. A.. (1) University of Southern California School of Medicine, Los Angeles, CA USA. Society for Neuroscience Abstracts, (2000)

Vol. 26, No. 1-2, pp. Abstract No.-151.22. print. Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience. ISSN: 0190-5295. Language: English. Summary Language: English.

AB Human JIP-1/**IB1**, a JNK-interacting protein, normally expressed in the CNS and pancreas, was initially identified as a scaffold of a JNK signaling module. However, in vivo stress functions of JIP-1/**IB1** are still largely unknown. Recently, JIP-1/**IB1** was shown to reduce cytokine-induced apoptosis of insulin secreting cells, suggesting an anti-apoptotic role. JIP-1/**IB1** serves as a substrate of **JNK3** in vitro, and has 10 potential proline-directed serine/threonine phosphorylation sites. To investigate if JIP-1/**IB1** is a phosphoprotein in vivo, we immunoprecipitated JIP-1/**IB1** from human neuroblastoma IMR-32 cells and analyzed its phosphorylation on western blots using phosphoprotein-specific antibodies. Our results indicated that JIP-1/**IB1** is a phosphoserine/phosphothreonine-containing protein but is negative for phosphotyrosine. Interestingly, UV irradiation-induced JNK activation was associated with a reduction of JIP-1/**IB1** phosphorylation. Co-expression of **JNK3** and MKK7, a JNK activator, caused apoptosis of Neuro-2A cells. When JIP-1/**IB1** was overexpressed, activated-JNK remained restricted to the cytoplasm and apoptosis was prevented. Our results strongly support an anti-apoptotic function for JIP-1/**IB1** in neuronal cells.

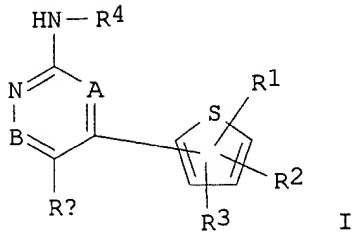
L8 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2000:135236 Document No.: PREV200000135236. Human JIP-1/**IB1** is a potential anti-apoptotic protein that functions through inhibition of **JNK3**. Dong, Z. (1); Zhang, Y. (1); Tashjian, V. (1); Zhou, L. (1); Miller, C. A. (1). (1) Dept. of Pathology, University of Southern California School of Medicine, Los Angeles, CA, 90033 USA. Society for Neuroscience Abstracts., (1999) Vol. 25, No. 1-2, pp. 1521. Meeting Info.: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999 Society for Neuroscience. ISSN: 0190-5295. Language: English. Summary Language: English.

```
=> s JNK inhibitor
L9          168 JNK INHIBITOR

=> s l9 and brain
L10          21 L9 AND BRAIN

=> dup remove l10
PROCESSING COMPLETED FOR L10
L11          13 DUP REMOVE L10 (8 DUPLICATES REMOVED)

=> d l11 1-13 cbib abs
```

L11 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2003 ACS
2002:814126 Document No. 137:325327 Preparation of thienyl-substituted pyrimidinyl, pyridinyl and triazinyl amines as inhibitors of c-Jun N-terminal kinases (JNK) and other protein kinases. Cao, Jingrong; Green, Jeremy; Moon, Young-Choon; Wang, Jian; Ledeboer, Mark; Harrington, Edmund; Gao, Huai (Vertex Pharmaceuticals Incorporated, USA). PCT Int. Appl. WO 2002083667 A2 20021024, 137 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG,

TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US11570 20020410. PRIORITY: US 2001-PV283621 20010413; US 2001-PV292974 20010523; US 2001-PV329440 20011015.

GI



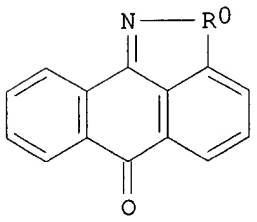
I

AB The present invention provides thienyl-substituted pyrimidinyl, pyridinyl and triazinyl amines (shown as I, e.g. 2-methylsulfanyl-5-(2-phenylaminopyrimidin-4-yl)-4-(4-chlorophenyl)thiophene-3-carbonitrile): or a pharmaceutically acceptable deriv. thereof, wherein A, B, Ra, R1, R2, R3 and R4 are as described in the specification. These compds. are inhibitors of protein kinase, particularly inhibitors of JNK, a mammalian protein kinase involved in cell proliferation, cell death and response to extracellular stimuli; Lck and Src kinase. The invention also provides pharmaceutical compns. comprising the inhibitors of the invention and methods of using those compns. in the treatment and prevention of various disorders. Although the methods of prepn. are not claimed, 42 example prepns. of intermediates and I are included. Results of JNK, Src and Lck inhibition are tabulated for many I.

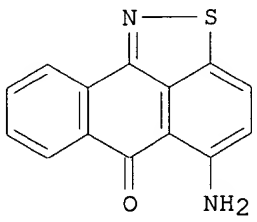
L11 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2003 ACS

2002:658099 Document No. 137:201301 Preparation of isothiazoloanthrones, isoxazoloanthrones, isoindolanthrones as **JNK inhibitors**. Sakata, Steven T.; Raymon, Heather K. (Signal Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2002066450 A2 20020829, 196 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US4283 20020213. PRIORITY: US 2001-PV269013 20010215; US 2002-71390 20020207.

GI



I



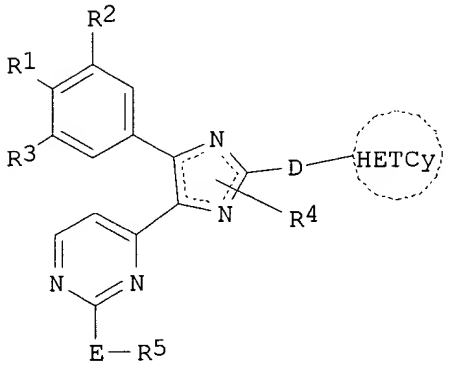
II

AB The title compds. [(un)substituted I; R0 = CH2, SO, O, SO2, S], useful for

treating or preventing a disorder alleviated by inhibiting Jun N-terminal kinase (JNK), were prepd. Thus, treating 1-aminoanthraquinone with NH4SCN in the presence of H2SO4 in DMSO followed by heating the thiocyanate-addn. intermediate in liq. ammonia in a bomb to 140.degree. for 5 h afforded II which showed IC50 of 1 .mu.M for JNK2 and 400 nM for JNK3.

L11 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2003 ACS
2002:615608 Document No. 137:169523 Preparation of azoles as **JNK inhibitors**. Ohkawa, Shigenori; Naruo, Kenichi; Miwatashi, Seiji; Kimura, Hiroyuki; Kawamoto, Tomohiro (Takeda Chemical Industries, Ltd., Japan). PCT Int. Appl. WO 2002062792 A1 20020815, 246 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP828 20020201. PRIORITY: JP 2001-27570 20010202.

GI

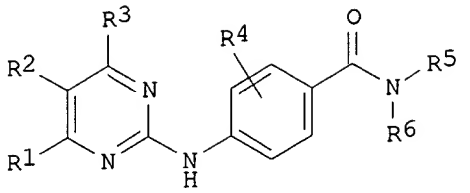


I

AB The title compds., e.g. I [R1 = F, OH, etc.; R2 = F, OH, etc.; R3 = H, F, etc.; R4 = (cycloalkyl-substituted) alkyl; R5 = alkyl, etc.; D = bond, alkylene; E = NH, etc.; HETCy = non-arom. heterocyclic ring; further details on said heterocyclic ring are given], are prepd. Compds. of this invention in vitro showed IC50 values of 0.03 .mu.M to 0.21 .mu.M against JNK1 kinase. In an in vitro test using THP-1 cells, compds. of this invention in vitro showed IC50 values of 0.002 .mu.M to 0.1 .mu.M against TNF-.alpha. prodn. Formulations are given.

L11 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2003 ACS
2002:449661 Document No. 137:33309 Preparation of anilinopyrimidines as JNK pathway inhibitors. Kois, Adam; MacFarlane, Karen J.; Satoh, Yoshitaka; Bhagwat, Shripad S.; Parnes, Jason S.; Palanki, Moorthy S. S.; Erdman, Paul E. (Signal Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2002046170 A2 20020613, 199 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US46402 20011205. PRIORITY: US 2000-PV251904 20001206.

GI



I

AB The title compds. [I; R1 = (un)substituted (hetero)aryl; R2 = H; R3 = H, alkyl; R4 = halo, OH, alkyl, alkoxy; R5, R6 = R8, (CH2)aCOR9, (CH2)aCO2R9, etc.; or NR5R6 = (un)substituted heterocycle; R8, R9 = H, alkyl, aryl, etc.; a = 0-4] having activity as inhibitors of the JNK pathway, were prepd. E.g., a multi-step synthesis of I [R1 = 4-ClC6H4; R2-R6 = H] having an IC50 of .ltoreq. 10 .mu.M in the JNK2 assay, was given. Such compds. I have utility in the treatment of a wide range of conditions that are responsive to inhibition of the JNK pathway. Thus, methods of treating such conditions are also disclosed, as are pharmaceutical compns. contg. one or more compds. of the above compds.

L11 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2003 ACS

2002:107318 Document No. 136:151163 Preparation of indazole derivatives as JNK enzyme inhibitors. Bhagwat, Shripad S.; Satoh, Yoshitaka; Sakata, Steven T. (Signal Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2002010137 A2 20020207, 412 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US23890 20010730. PRIORITY: US 2000-PV221799 20000731.

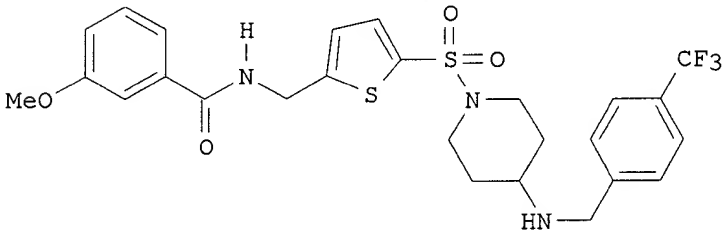
AB Indazole derivs., 3-R1A-5-R2-1H-indazoles (1), having activity as selective inhibitors of JNK are disclosed. In 1: A is a direct bond, -(CH2)a-, -(CH2)bCH:CH(CH2)c-, or -(CH2)bC.tplbond.C(CH2)c-; R1 is aryl, heteroaryl or heterocycle fused to Ph, each being optionally substituted with 1-4 R3; R2 is -R3, -R4, -(CH2)bC(O)R5, -(CH2)bC(:O)OR5, -(CH2)bC(O)NR5R6, -(CH2)bC(O)NR5(CH2)cC(O)R6, -(CH2)bNR5C(O)R6, -(CH2)bNR5C(O)NR6R7, -(CH2)bNR5R6, -(CH2)bOR5, -(CH2)bSOdR5 or -(CH2)bSO2NR5R6. A is 1-6; b and c are the same or different and are 0-4; d is 0-2. R3 is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, -C(O)OR8, -C(O)R8, -C(O)NR8R9, -C(O)NR8OR9, -SO2NR8R9, -NR8SO2R9, -CN, -NO2, -NR8R9, -NR8C(O)R9, -NR8C(O)(CH2)bOR9, -NR8C(O)(CH2)bR9, -O(CH2)bNR5R9, or heterocycle fused to Ph. R4 is alkyl, aryl, arylalkyl, heterocycle or heterocyclealkyl, each being optionally substituted with 1-4 R3, or R4 is halogen or hydroxy. R5, R6and R7 are the same or different and are H, alkyl, aryl, arylalkyl, heterocycle or heterocyclealkyl, wherein each of R5, R6 and R7 are optionally substituted with 1-4 R3. R8 and R9 are the same or different and at each occurrence independently H, alkyl, aryl, arylalkyl, heterocycle, or heterocyclealkyl, or R8 and R9 taken together with the atom or atoms to which they are bonded form a heterocycle,

wherein each of R8, R9, and R8 and R9 taken together to form a heterocycle are optionally substituted with 1-4 R3 with the proviso that: when A is a direct bond and R1 is Ph, R2 is not Me, methoxy, C(O)CH3 or C(O)H; when A is a direct bond and R1 is 4-Me-Ph, R2 is not Me; when A is a direct bond and R1 is 4-F-Ph, R2 is not trifluoromethyl; when A is a direct bond or -C.tplbond.C- and R1 is Ph, R2 is not -COOEt; and when A is a direct bond and R1 is 6,7-dimethoxyisoquinolin-1-yl, R2 is not hydroxy. Such compds. have utility in the treatment of a wide range of conditions that are responsive to JNK inhibition. Thus, methods of treating such conditions are also disclosed, as are pharmaceutical compns. contg. one or more compds. of the above compds. Many of the claimed compds. have IC50 values .ltoreq.0.5 .mu.M in the JNK2 assay, e.g. 5-[3-(4-fluorophenyl)-1H-indazol-5-yl]-2H-1,2,3,4-tetrazole. Although the methods of prepn. are not claimed, >400 example prepns. are included.

L11 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2003 ACS

2002:253021 Document No. 136:279348 Preparation of pharmaceutically active sulfonamides bearing both lipophilic and ionizable moieties as inhibitors of protein Jun kinases. Halazy, Serge; Church, Dennis; Camps, Montserrat; Rueckle, Thomas; Gotteland, Jean Pierre; Biamonte, Marco; Arkinstall, Stephen (Applied Research Systems ARS Holding N.V., Neth. Antilles). Eur. Pat. Appl. EP 1193268 A1 20020403, 44 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 2000-810887 20000927.

GI



II

AB The title compds. Ar1C(:X)NR1(CH2)nAr2SO2Y [I; Ar1, Ar2 = (un)substituted aryl, heteroaryl; X = O, S, preferably O; R1 = H, alkyl, or R1 forms (un)substituted 5-6 membered (un)satd. ring with Ar1; n = 0-5, preferably between 1-3 and most preferred 1; Y = (un)substituted 4-12 membered satd. cyclic or bicyclic alkyl which is substituted with at least one ionizable moiety to which a lipophilic chain is attached and which is contg. at least one N atom, whereby one N atom within said ring is forming a bond with the sulfonyl group thus providing a sulfonamide] which are efficient modulators of the JNK pathway, in particular efficient and selective inhibitors of JNK 2 and 3, were prepd. and formulated. E.g., a multi-step synthesis of II which showed IC50 of 0.04 .mu.M against JNK3, was given.

L11 ANSWER 7 OF 13 MEDLINE DUPLICATE 1

2002607368 Document Number: 22201813. PubMed ID: 12213570. The c-Jun N-terminal kinases in cerebral microglia: immunological functions in the **brain**. Hidding Ute; Mielke Kirsten; Waetzig Vicki; Brecht Stephan; Hanisch Uwe; Behrens Alexander; Wagner Erwin; Herdegen Thomas. (Institute of Pharmacology, Hospitalstrasse 4, 24105 Kiel, Germany.) BIOCHEMICAL PHARMACOLOGY, (2002 Sep) 64 (5-6) 781-8. Journal code: 0101032. ISSN: 0006-2952. Pub. country: England: United Kingdom. Language: English.

AB The c-Jun N-terminal kinases (JNKs) exert a pleiotrophy of physiological and pathological actions. This is also true for the immune system. Disruption of the JNK locus results in substantial functional deficits of peripheral T-cells. In contrast to circulating immune cells and the role of p38, the presence and function of JNKs in the immune cells of the

brain remain to be defined. Here, we report on the expression and activation of JNKs in cultivated microglia from neonatal rats and from mice with targeted disruption of the JNK locus and the N-terminal mutation of c-Jun (c-JunAA), respectively. JNK1, 2 and 3 mRNA and proteins were all expressed in microglia. Following stimulation with LPS (100 ng/mL), a classical activator of microglia, JNKs were rapidly activated and this activation returns to basal levels within 4 hr. Following LPS and other stimuli such as thrombin (10-50 unit/mL), the activation of JNKs went along with the N-terminal phosphorylation of c-Jun which persisted for at least 8 hr. Indirect inhibition of JNK by CEP-11004 (0.5-2 microM), an inhibitor of mixed-lineage kinases (MLK), reduced the LPS-induced phosphorylation of both, JNK and c-Jun, by around 50%, and attentuated the LPS-induced the alterations in microglial morphology. Finally, JNKs are involved in the control of cytokine release since both, incubation with CEP-11004 and disruption of the JNK1 locus enhanced the release of TNFalpha, IL-6 and IL-12. Our findings provide insight in so far unknown functions of JNKs in cerebral immune cells. These observations are also important for the wide spread efforts to develop **JNK-inhibitors** as neuroprotective drugs which, however, might trigger pro-inflammatory processes.

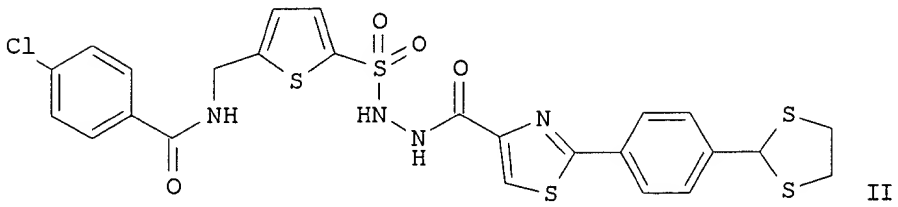
L11 ANSWER 8 OF 13 MEDLINE DUPLICATE 2
2002228747 Document Number: 21917855. PubMed ID: 11919515.
Mitogen-activated protein kinase inhibition in traumatic **brain** injury: in vitro and in vivo effects. Mori Tatsuro; Wang Xiaoying; Jung Jae-Chang; Sumii Toshihisa; Singhal Aneesh B; Fini M Elizabeth; Dixon C Edward; Alessandrini Alessandro; Lo Eng H. (Neuroprotection Research Laboratory, Department of Radiology, Massachusetts General Hospital, Charlestown, Massachusetts, USA.) JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, (2002 Apr) 22 (4) 444-52. Journal code: 8112566. ISSN: 0271-678X. Pub. country: United States. Language: English.

AB The authors provide the first in vitro and in vivo evidence that perturbations in mitogen-activated protein kinase (MAPK) signal-transduction pathways are involved in the pathophysiology of traumatic **brain** injury. In primary rat cortical cultures, mechanical trauma induced a rapid and selective phosphorylation of the extracellular signal-regulated kinase (ERK) and p38 kinase, whereas there was no detectable change in the c-jun N-terminal kinase (JNK) pathway. Treatment with PD98059, which inhibits MAPK/ERK 1/2, the upstream activator of ERK, significantly increased cell survival in vitro. The p38 kinase and **JNK inhibitor** SB203580 had no protective effect. Similar results were obtained in vivo using a controlled cortical impact model of traumatic injury in mouse **brain**. Rapid and selective upregulation occurred in ERK and p38 pathways with no detectable changes in JNK. Confocal immunohistochemistry showed that phospho-ERK colocalized with the neuronal nuclei marker but not the astrocytic marker glial fibrillary acidic protein. Inhibition of the ERK pathway with PD98059 resulted in a significant reduction of cortical lesion volumes 7 days after trauma. The p38 kinase and **JNK inhibitor** SB203580 had no detectable beneficial effect. These data indicate that critical perturbations in MAPK pathways mediate cerebral damage after acute injury, and further suggest that ERK is a novel therapeutic target in traumatic **brain** injury.

L11 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2003 ACS
2002:125925 Document No. 136:151160 Preparation of N-thienylsulfonylthiazolecarbohydrazides and analogs as c-Jun N-terminal kinase inhibitors. Arkinstall, Stephen; Halazy, Serge; Church, Dennis; Camps, Montserrat; Rueckle, Thomas; Gotteland, Jean-Pierre; Biamonte, Marco (Applied Research Systems ARS Holding N.V., Neth. Antilles). PCT Int. Appl. WO 2001023382 A1 20010405, 76 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,

JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-IB1381 20000928. PRIORITY: EP 1999-810870 19990928.

GI



II

AB RC(:X1)NR1(CH2)nZSO2NR2NR3C(:X2)R4 [I; R = (un)substituted (hetero)aryl; R1, R2, and R3 = H or alkyl; or RR1 and/or R2R3 = atoms to complete a ring; R4 = (un)substituted alkyl or heterocyclyl; X1 and X2 = O or S; Z = (un)substituted (hetero)arylene; n = 0-5] were prepd. as c-Jun N-terminal kinase (**JNK**) **inhibitors**, esp. JNK2 or JNK3 inhibitors. Thus, 2-thiophenemethanamine was amidated by 4-ClC6H4COCl (98%) and the chlorosulfonated product (63%) amidated by 2-[4-(1,3-dithiolan-2-yl)phenyl]thiazole-4-carbohydrazide to give title compd. II (80%). The latter exhibited selective inhibitory effect for JNK2 and JNK3 compared with p38 kinase and ERK2 protein kinase with IC50 values of 0.21 .mu.M, 0.37 .mu.M, >30 .mu.M, and >30 .mu.M, resp. Thus, I are useful for the treatment of neuronal disorders, autoimmune diseases, cancer, and cardiovascular disease.

L11 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

2001:574284 Document No.: PREV200100574284. The **JNK inhibitor**, SPC9766 is efficacious in models of epilepsy and stroke. Raymon, H. K. (1); Omholt, P. E. (1); Celeridad, M. T. (1); Sakata, S. T. (1); O'Leary, E. C. (1); Bhagwat, S. S. (1); Stein, B. (1); Anderson, D. W. (1). (1) Signal Research Division, Celgene Corp., San Diego, CA USA. Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2025. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001 ISSN: 0190-5295. Language: English. Summary Language: English.

AB Activation of the c-Jun N-terminal kinase (JNK) pathway plays a role in apoptotic neuronal cell death. We hypothesize that blockade of JNK(s) will prevent neuronal cell death in a variety of systems. Previously, we reported the neuroprotective effects of the selective **JNK inhibitor**, SPC9766 in a cellular model of dopamine neurotoxicity. In the present study, we have demonstrated that SPC9766 is efficacious in rodent models of epilepsy and stroke. We examined the effect of SPC9766 on kainic acid-induced seizures since it had been shown that the JNK3 knockout mouse is resistant to kainic acid and to seizure-induced neuronal cell death (Yang et al., 1997). SPC9766 (20 ug, i.c.v.) injected immediately prior to the administration of kainic acid (10 mg/kg s.c.) blocked seizure activity. This effect was observed up to 4 hrs after kainic acid administration. We also assessed the effect of SPC9766 in a model of transient **brain** ischemia. Rats were subjected to 2 hrs of ischemia and either 24 or 72 hrs of reperfusion. Compound was infused i.c.v for 3 hrs, starting 15 min after the onset of ischemia. There was a 29% and 34% reduction in infarct volume at 24 and 72 hrs, respectively, in animals treated with SPC9766 compared to untreated vehicle control. SPC9766 decreased the number of TUNEL positive cells at both timepoints

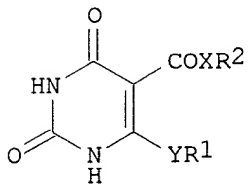
indicating a decline in the number of apoptotic cells in the region of the infarct. Taken together, these data point to a possible role of JNK in neuronal apoptosis and strengthen the hypothesis that JNKs are potential therapeutic targets in diseases and disorders of the nervous system.

L11 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2003 ACS
2002:41807 Document No. 137:163005 Inhibitors of the JNK signaling pathway. Harper, Sarah J.; LoGrasso, Philip (Department of Pharmacology, Neuroscience Research Centre, Harlow, Essex, CM20 2QR, UK). Drugs of the Future, 26(10), 957-973 (English) 2001. CODEN: DRFUD4. ISSN: 0377-8282. Publisher: Prous Science.

AB A review. A review on some endogenous inhibitors of the jun-N-terminal kinase (JNK) pathway, such as growth factors, JNK-interacting proteins and heat shock protein 72. Various chem. inhibitors of the JNK pathway, such as CEP-1347, a mixed-lineage kinase (MLK) inhibitor, SB-203580 and SB-202190, combined p38 and **JNK inhibitors** and SPC0009766, are also discussed. The JNK signal transduction pathwy is activated in different cell types and in response to different stressful stimuli. Inhibition of JNK promotes cell survival, particularly in neurons. The best prospects for **JNK inhibitors** in the clinic would be for a neuronal target such as stroke or Parkinson's disease, where a specific JNK3 inhibitor could be given wihtout effects on non-neuronal cells.

L11 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2003 ACS
2000:881129 Document No. 134:42135 Preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases.. Salituro, Francesco; Bemis, Guy; Green, Jeremy; Fejzo, Jasna; Xie, Xiaoling (Vertex Pharmaceuticals Incorporated, USA). PCT Int. Appl. WO 2000075118 A1 20001214, 37 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US15248 20000602. PRIORITY: US 1999-PV137523 19990603.

GI



I

AB Title compds. [I; Y = O, NH, NR, S, SO, SO2; X = O, NH, NR; R1, R2 = H, (substituted) alkyl, alkenyl, (arom.) (bicyclic) carbocyclyl, heterocyclyl; R = alkyl, alkenyl, (arom.) (bicyclic) carbocyclyl, heterocyclyl], were prepd. as inhibitors of c-JUN N-terminal kinases. Thus, I (R1Y, R2X = PhNH) inhibited JNK3 with IC50 <1 .mu.M.

L11 ANSWER 13 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2001:120755 Document No.: PREV200100120755. The **JNK inhibitor**, SPC0009766 reverses neurotoxin-induced damage in cultures of rat dopaminergic neurons. Raymon, H. K. (1); Celeridad, M. T.; Sakata, S. T.; Bennett, B. L.; Satoh, Y.; Bhagwat, S. S.; Manning, A. M.. (1) Signal Pharmaceuticals, Inc, San Diego, CA USA. Society for

Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-700.10. print. Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience. ISSN: 0190-5295. Language: English. Summary Language: English.

AB The c-Jun N-terminal kinase (JNK) pathway has been implicated in mediating apoptotic neuronal cell death. Of the three genes encoding the JNKs, JNK3 is highly expressed in the **brain**. Disruption of this gene results in resistance to kainic acid-induced seizures and prevention of hippocampal neuronal cell death. We hypothesize that inhibitors of JNK3 will block neuronal cell death induced by a variety of insults. In the present study, we have examined whether the **JNK inhibitor**, SPC0009766 can reverse 6-hydroxydopamine (6-OHDA)-induced damage of dopaminergic neurons in vitro. Ventral mesencephalic dopaminergic neurons were isolated from 14-15 day rat embryos. At 7 days in vitro, cells were pretreated for 40 min with varying concentrations of SPC0009766, prior to the addition of 30 muM 6-OHDA. Twenty-four hrs later, cultures were assayed for (3H)dopamine uptake and c-jun phosphorylation. 6-OHDA treatment resulted in a 60% decrease in (3H)dopamine uptake and induced phosphorylation of c-jun, as determined by Western analysis. Treatment with SPC0009766 dose-dependently increased dopamine uptake, attaining control values at 30 muM. The IC50 for this effect was 15 muM. c-Jun phosphorylation was blocked by 30 muM SPC0009766, indicating the expected mechanism of action for this type of compound. Taken together, these data point to a possible role of JNK in dopaminergic neurotoxicity and support the hypothesis that JNKs are a potential target for Parkinson's disease therapeutics. Future studies will focus on determining the efficacy of this class of compound in animal models of Parkinson's disease.

```
=> s (miller c?/au or dong z?/au or zhang?/au)
L12     438587 (MILLER C?/AU OR DONG Z?/AU OR ZHANG?/AU)

=> s l12 and JUN binding protein
L13           0 L12 AND JUN BINDING PROTEIN

=> s l12 and JNK binding protein
L14           0 L12 AND JNK BINDING PROTEIN

=> s l12 and "JNK-3"
L15           2 L12 AND "JNK-3"

=> dup remove l15
PROCESSING COMPLETED FOR L15
L16           2 DUP REMOVE L15 (0 DUPLICATES REMOVED)

=> d l16 1-2 cbib abs
```

L16 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1999:79737 Document No.: PREV199900079737. Stress-induced tau phosphorylation by **JNK-3** in vivo and in vitro. Kim, O. J.; Kumagae, Y.; **Miller, C. A.**. Dep. Pathol., Univ. South. Calif. Sch. Med., Los Angeles, CA 90033 USA. Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 1372. Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 2 Los Angeles, California, USA November 7-12, 1998 ISSN: 0190-5295. Language: English.

L16 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1998:247223 Document No.: PREV199800247223. Up-regulation of **JNK-3**, human SAPKbeta, after ischemia in cultured neuroblastoma cells. Kumagae, Yoshihiro (1); **Zhang, Yan; Miller, Carol A.**. (1) Neurosci. Res. Labs, Sankyo Co., Shinagawa, Tokyo Japan. Japanese Journal of Pharmacology, (1998) Vol. 79, No. SUPPL. 1, pp. 271P. Meeting

Info.: 71st Annual Meeting of the Japanese Pharmacological Society Kyoto, Japan March 23-26, 1998 The Japanese Pharmacological Society. ISSN: 0021-5198. Language: English.

=> d his

(FILE 'HOME' ENTERED AT 15:15:50 ON 02 JAN 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 15:16:03 ON 02 JAN 2003

```
L1       7041944 S TREATMENT
L2          4675 S L1 AND NEUROLOGICAL DISORDER
L3           645 S L2 AND STROKE
L4             1 S L3 AND JNK
L5           384 S JNK3
L6             1 S L5 AND JIP1
L7             3 S L5 AND IB1
L8             3 DUP REMOVE L7 (0 DUPLICATES REMOVED)
L9           168 S JNK INHIBITOR
L10           21 S L9 AND BRAIN
L11           13 DUP REMOVE L10 (8 DUPLICATES REMOVED)
L12       438587 S (MILLER C?/AU OR DONG Z?/AU OR ZHANG?/AU)
L13            0 S L12 AND JUN BINDING PROTEIN
L14            0 S L12 AND JNK BINDING PROTEIN
L15            2 S L12 AND "JNK-3"
L16            2 DUP REMOVE L15 (0 DUPLICATES REMOVED)
```

=> s l12 and SAPK
L17 91 L12 AND SAPK

=> dup remove l17
PROCESSING COMPLETED FOR L17
L18 27 DUP REMOVE L17 (64 DUPLICATES REMOVED)

=> d l18 1-27 cbib abs

L18 ANSWER 1 OF 27 MEDLINE DUPLICATE 1
2002654564 Document Number: 22302031. PubMed ID: 12223491. SUMO-1 modification of the C-terminal KVEKVD of Axin is required for JNK activation but has no effect on Wnt signaling. Rui Hong-Liang; Fan Ernest; Zhou Hai-Meng; Xu Zhen; **Zhang Yi**; Lin Sheng-Cai. (Department of Biochemistry, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Nov 8) 277 (45) 42981-6. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Axin is a multifunctional protein, regulating Wnt signaling and the c-Jun N-terminal/stress-activated protein kinase (JNK/**SAPK**) pathway as well as tumorigenesis. In the present study, we found that Axin interacts with three SUMO-1 (small ubiquitin-related modifier) conjugating enzymes 3 (E3), PIAS1, PIASxbeta, and PIASy. The extreme C-terminal six amino acid residues of Axin are critical for the Axin/E3 interaction as deletion of the six residues (AxinDeltaC6) completely abolished the ability of Axin to interact with E3 enzymes. AxinDeltaC6 also failed to activate JNK, although it was intact in both its interaction with MEKK1 and homodimerization. Consistent with the presence of a doublet of the KV(E/D) sumoylation consensus motif at the C-terminal end (KVEKVD), we found that Axin is heavily sumoylated. Deletion of the C-terminal six amino acids drastically reduced sumoylation, indicating that the C-terminal six amino acids stretch is the main sumoylation site for Axin. Sumoylation-defective mutants failed to activate JNK but effectively destabilized beta-catenin and attenuated LEF1 transcriptional activity. In addition, we show that dominant negative Axin mutants blocked PIAS-mediated JNK activation, in

accordance with the requirement of sumoylation for Axin-mediated JNK activation. Taken together, we demonstrate that sumoylation plays a role for Axin to function in the JNK pathway.

L18 ANSWER 2 OF 27 MEDLINE DUPLICATE 2
2002208992 Document Number: 21938918. PubMed ID: 11942415. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. **Zhang Wei**; Liu Hui Tu. (The Key Laboratory of Cell Proliferation and Regulation Biology of Ministry of Education, College of Life Sciences, Beijing Normal University, China.) CELL RESEARCH, (2002 Mar) 12 (1) 9-18. Journal code: 9425763. ISSN: 1001-0602. Pub. country: China. Language: English.
AB MAPK families play an important role in complex cellular programs like proliferation, differentiation, development, transformation, and apoptosis. At least three MAPK families have been characterized: extracellular signal-regulated kinase (ERK), Jun kinase (JNK/**SAPK**) and p38 MAPK. The above effects are fulfilled by regulation of cell cycle engine and other cell proliferation related proteins. In this paper we discussed their functions and cooperation with other signal pathways in regulation of cell proliferation.

L18 ANSWER 3 OF 27 MEDLINE
2001372342 Document Number: 21322828. PubMed ID: 11429707. Contrasting roles of NF-kappaB and JNK in arsenite-induced p53-independent expression of GADD45alpha. Chen F; **Zhang Z**; Leonard S S; Shi X. (The Health Effects Laboratory Division, National Institute for Occupational Safety and Health, 1095 Willowdale Road, Morgantown, West Virginia, WV 26505, USA.) ONCOGENE, (2001 Jun 14) 20 (27) 3585-9. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.
AB Growth arrest and DNA damage-inducible protein 45alpha (GADD45alpha) is an important cell cycle checkpoint protein that arrests cells at G2/M phase by inhibiting the activity of G2-specific kinase, cyclin B/p34cdc2. We report here that arsenite induces GADD45alpha expression in a p53-independent fashion and that this GADD45alpha induction by arsenite is regulated by NF-kappaB and c-Jun-N-terminal kinase (JNK) oppositely. In human bronchial epithelial cells overexpressing a kinase-mutated form of IkappaB kinase beta (IKKbeta-KM), the activation of NF-kappaB was inhibited. However, the G2/M cell cycle arrest and expression of GADD45alpha was substantially enhanced in response to arsenite in these cells. Expression of a dominant-negative mutant of SEK1 that blocks JNK activation decreased arsenite-induced GADD45alpha expression. Analysis of GADD45alpha expression in both wild-type and p53-/- fibroblasts indicated that the induction of GADD45alpha by arsenite was independent of the status of p53 protein.

L18 ANSWER 4 OF 27 MEDLINE
2001641837 Document Number: 21551408. PubMed ID: 11694646. Specific amino acid deficiency alters the expression of genes in human melanoma and other tumor cell lines. Meadows G G; **Zhang H**; Ge X. (Cancer Prevention and Research Center, Department of Pharmaceutical Sciences, College of Pharmacy, Washington State University, Pullman, WA 99164-6510, USA.. meadows@wsu.edu) . JOURNAL OF NUTRITION, (2001 Nov) 131 (11 Suppl) 3047S-50S. Journal code: 0404243. ISSN: 0022-3166. Pub. country: United States. Language: English.
AB This study determined the effect of tyrosine (Tyr) and phenylalanine (Phe) deprivation on protein expression and phosphorylation of mitogen-activated protein kinase kinase 4 (MKK4)/stress-activated protein/Erk kinase (SEK1), a metastasis suppressor gene. Differential display and suppressive subtractive hybridization techniques identified genes modulated by Tyr and Phe deprivation. Expression of MKK4/SEK1 protein varied widely among human A375, A375SM and SB2 melanoma, PC-3 and DU145 prostate cancer, and MDA-MB-231 breast cancer cell lines and within the different lines. Phosphorylation of the MKK4/SEK1 protein similarly varied. No differences

in MKK4/SEK1 gene expression or in the 41 other metastasis and tumor suppressor genes were found in A375 melanoma cells cultured in Tyr- and Phe-deprived media. A number of up-regulated and down-regulated genes in A375 melanoma cells were identified by differential display and suppressive subtractive hybridization that were pertinent to regulation of cytoskeletal organization, cell movement, gene transcription and metastasis. Two tumor marker genes, the gene for enolase and FUS/CHOP, were down-regulated by Tyr and Phe deprivation. This study shows that tumor cells display heterogeneity in their response to deprivation of Tyr and Phe and that these amino acids may be signaling molecules that regulate gene expression and function in tumor cells.

L18 ANSWER 5 OF 27 MEDLINE DUPLICATE 3

2001695697 Document Number: 21610829. PubMed ID: 11745435. Aberrant expression of Smad4 results in resistance against the growth-inhibitory effect of transforming growth factor-beta in the SiHa human cervical carcinoma cell line. Lee S; Cho Y S; Shim C; Kim J; Choi J; Oh S; Kim J; **Zhang W**; Lee J. (Molecular Therapy Research Center, Sungkyunkwan University, Seoul, South Korea.) INTERNATIONAL JOURNAL OF CANCER, (2001 Nov15) 94 (4) 500-7. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB Smad proteins activated by TGF-beta form complexes with Smad4. Upon activation, these complexes translocate to the nucleus of the cell, where they induce transcription of genes related to inhibition of cell growth, cell differentiation and apoptosis. We investigated the role of Smads in the TGF-beta-mediated signal-transduction cascade in 4 human cervical cancer cell lines: HeLa, Caski, HT-3 and SiHa. Based on our results, SiHa cells show low mRNA expression of mutated Smad4 (Gly(230)Ala, Ala(488)Val) and of Smads 2, 3, 5 and 6. SiHa cells were likewise defective in TGF-beta signaling, as evidenced by a lack of significant growth inhibition following TGF-beta treatment. In addition, TGF-beta did not induce transcription of the PAI-1 gene or change Smad protein levels. Introduction of Smad3 and/or Smad4 into SiHa cells restored TGF-beta signaling, as determined by activation of the 3TP-lux reporter gene and by prominent apoptotic cell death with PAI-1 induction. Analysis of the downstream targets activated by TGF-beta yielded rapid activation of p38 with subsequent phosphorylation of the transcription factor ATF-2 but unchanged **SAPK**/JNK activation in the 4 cervical cancer cell lines. Our findings demonstrate that (i) decrease of Smad4 mRNA expression is closely associated with defective TGF-beta response and lack of growth inhibition, (ii) activation of PAI-1 by TGF-beta may be Smad4-dependent and (iii) the Smad and the p38 cascades are triggered by TGF-beta independently of each other in human cervical cancer.

L18 ANSWER 6 OF 27 BIOSIS DUPLICATE 4

2001:431039 Document No.: PREV200100431039. Signal transduction pathway of in human B lymphoma apoptosis induced by anti-IgM Daudi cell line. **Zhang Fan (1)**; Zhu Hongxia (1); Liu Shuang (1); et al. (1) Inq.: Xu Ningzhi, Laboratory of Cell and Molecular Biology, Cancer Institute, Chinese Academy of Medical Science, Beijing, 100021: xningzhi@public.bta.net.cn, xningzhi@public.bta.net.cn, xningzhi@public.bta.net.cn China. Zhonghua Weishengwuxue He Mianyixue Zazhi, (July, 2001) Vol. 21, No. 4, pp. 409-412. print. ISSN: 0254-5101. Language: Chinese. Summary Language: Chinese; English.

AB Objective: To investigate the mechanism of apoptosis of human B lymphoma Daudi cell line mediated by B cell antigen receptor (BCR). Methods: Cell growth was examined by 3H-TdR incorporation, cell cycle and apoptosis were analysed by fluorescence activated cell sorter(FACS). The activation of signal molecules in Daudi cell stimulated by anti-IgM antibody was measured by Western blot. Results: anti-IgM antibody induced human B lymphoma Daudi cell towards apoptosis. The number of apoptotic cells was

correlated with the concentration of anti-IgM antibody. The result of Western blot indicated that the phosphorylation level of the tyrosine protein in Daudi cell was related to the concentration of the anti-IgM stimulation. After stimulating 48 to 72 hours, much tyrosine proteins and phosphorylation return to low phosphorylation level or dephosphorylation. Even though the level of JNK1 and ERK2 protein changed little, but the level of phosphorylation at its 63/73 serine and total protein of c-Jun, one of downstream molecules from JNK, increased immediately and kept for long time. Conclusion: anti-IgM antibody can induce apoptosis of Daudi cell, and activation of JNK/**SAPK** can also be stimulated by anti-IgM antibody in Daudi cell. The JNK/**SAPK** pathway may be involved in the apoptosis of Daudi was induced by anti-IgM antibody.

L18 ANSWER 7 OF 27 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5

2002:133177 Document No.: PREV200200133177. RB-associated protein 46 (RbAp46) induces apoptosis through activation of GADD45 and JNK/**SAPK** -dependent pathway. **Zhang, Tengfei (1)**; Guan, LiShuang (1); Yu, ShuiQing (1); Wang, ZhaoYi (1). (1) Medicine/Growth Regulation, Beth Israel Deaconess Medical Center, 21-27 Burlington Ave., RM516, Boston, MA, 02134 USA. Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 152a-153a. http://www.molbiolcell.org/. print. Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001 ISSN: 1059-1524. Language: English.

L18 ANSWER 8 OF 27 MEDLINE DUPLICATE 6

2001321762 Document Number: 21079420. PubMed ID: 11211936. Retinoic acid-induced blr1 expression requires RARalpha, RXR, and MAPK activation and uses ERK2 but not JNK/**SAPK** to accelerate cell differentiation. Battle T E; Roberson M S; **Zhang T**; Varvayanis S; Yen A. (Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, USA. traci. battle@dfci.harvard.edu) . EUROPEAN JOURNAL OF CELL BIOLOGY, (2001 Jan) 80 (1) 59-67. Journal code: 7906240. ISSN: 0171-9335. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Upstream signaling requirements of retinoic acid (RA)-induced blr1 expression and downstream signaling consequences of blr1 over-expression in a human myeloid leukemia cell line demonstrate that mitogen-activated protein kinase (MAPK) signaling complexes are involved in both avenues. RA-induced myeloid differentiation and G1/G0 growth arrest of HL-60 cells is known to require the activation of the RARalpha and RXR retinoid receptors, as well as activation of the MAPK, ERK2. Transcriptional activation of the Burkitt's lymphoma receptor 1 (blr1) gene occurs early during RA-induced differentiation of HL-60 cells and requires these same three activating processes. The use of retinoid ligands that activate either the RARalpha or the RXR retinoid receptors revealed that blr1 mRNA induction was detectable only when both RARalpha and RXR were activated. Neither the RARalpha nor RXR selective ligands alone induced expression of blr1, but the combination of the two ligands induced the expression of blr1 to the same extent as RA. The MAPKK (MEK) inhibitor, PD98059, was used to determine whether extracellular signal-regulated kinase (ERK2) activation was necessary for induction of blr1 mRNA. PD98059 inhibited induced blr1 mRNA expression, due to RA or activated RARalpha plus RXR ligands, indicating that ERK2 activation is necessary for blr1 mRNA expression. Previous studies showed that ectopic expression of blr1 also caused increased MAPK activation, in particular ERK2, and subsequently accelerated RA-induced differentiation and G1/G0 growth arrest. Inhibition of ERK2 activation inhibited differentiation of blr1 transfectants, suggesting that the accelerated differentiation reflected blr1-enhanced ERK2 activation. The present data also demonstrate that ectopic expression of blr1 increased JNK/**SAPK** activity, but JNK/ **SAPK** activation was not needed for accelerated RA-induced differentiation and

growth arrest. The results show that the signals known to be required for HL-60 differentiation, activated RARalpha, RXR, and ERK2, are necessary for blr1 mRNA expression. Downstream consequences of blr1 overexpression include enhanced MAPK signaling.

L18 ANSWER 9 OF 27 MEDLINE DUPLICATE 7
2001027450 Document Number: 20493615. PubMed ID: 10918063. Phorbol ester-induced expression of airway squamous cell differentiation marker, SPRR1B, is regulated by protein kinase Cdelta /Ras/MEKK1/MKK1-dependent/AP-1 signal transduction pathway. Vuong H; Patterson T; Shapiro P; Kalvakolanu D V; Wu R; Ma W Y; **Dong Z**; Kleeberger S R; Reddy S P. (Department of Environmental Health Sciences, The Johns Hopkins University School of Public Health, Baltimore, Maryland 21205, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 13) 275 (41) 32250-9. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The transcriptional induction of SPRR1B by phorbol 12-myristate 13-acetate (PMA) is mainly mediated by the first -152-base pair 5'-flanking region containing two functional AP-1 sites. In this study, we have analyzed the signaling pathways that mediate the induction in tracheobronchial epithelial cells. PKC inhibitor ablated PMA-stimulated expression of endogenous SPRR1B and reporter gene expression driven by SPRR1B promoter. PKC activator promoted the transcription. The dominant negative protein kinase Cdelta (dn-PKCdelta) and rottlerin (PKCdelta inhibitor) completely suppressed PMA-stimulated promoter activity. dn-Ras or dn-MEKK1 inhibited PMA-stimulated promoter activity, while their corresponding constitutively active mutants augmented it. dn-c-Raf-1 did not have any effect on reporter gene expression. Since MEKK1 activates multiple parallel pathways, we examined involvement of JNK/**SAPK**, p38, and MKK1 in promoter regulation. Co-expression of the dominant negative forms of MKK4, MKK7, JNK/**SAPK**, MKK3, MKK6, or p38alpha did not suppress PMA-stimulated reporter gene expression. However, MKK1 inhibitors UO126 and PD98095 suppressed gene expression. Consistent with this, expression of dn-MKK1 strongly suppressed PMA-stimulated promoter activity, while the constitutively active MKK1 augmented it. However, MKK1-mediated induction of SPRR1B probably does not depend on extracellular signal-regulated kinases 1 and 2, suggesting the requirement of another kinase(s). dn-c-Jun mutants abolished PMA-stimulated expression supporting an important role for AP-1 proteins in SPRR1B expression. Together, these results suggest that a PKCdelta/Ras/MEKK1/MKK1-dependent/AP-1 pathway regulates the PMA-inducible expression of the SPRR1B in tracheobronchial epithelial cells.

L18 ANSWER 10 OF 27 MEDLINE DUPLICATE 8
2000428462 Document Number: 20387405. PubMed ID: 10829020. Dimerization choices control the ability of axin and dishevelled to activate c-Jun N-terminal kinase/stress-activated protein kinase. **Zhang Y**; Neo S Y; Han J; Lin S C. (Regulatory Biology Laboratory, Institute of Molecular and Cell Biology, National University of Singapore, 30 Medical Drive, Singapore 117609, Republic of Singapore.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Aug 11) 275 (32) 25008-14. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Axin and Dishevelled are two downstream components of the Wnt signaling pathway. Dishevelled is a positive regulator and is placed genetically between Frizzled and glycogen synthase kinase-3beta, whereas Axin is a negative regulator that acts downstream of glycogen synthase kinase-3beta. It is intriguing that they each can activate the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/**SAPK**) when expressed in the cell. We set out to address if Axin and Dishevelled are functionally cooperative, antagonistic, or entirely independent, in terms of the JNK activation event. We found that in contrast to Axin, Dvl2 activation of JNK does not require MEKK1, and complex formation between Dvl2 and Axin is independent of Axin-MEKK1 binding. Furthermore, Dvl2-DIX

and Dvl2-DeltaDEP proteins deficient for JNK activation can attenuate Axin-activated JNK activity by disrupting Axin dimerization. However, Axin-DeltaMID, Axin-DeltaC, and Axin-CT proteins deficient for JNK activation cannot interfere with Dvl2-activated JNK activity. These results indicate that unlike the strict requirement of homodimerization for Axin function, Dvl2 can activate JNK either as a monomer or homodimer/heterodimer. We suggest that there may be a switch mechanism based on dimerization combinations, that commands cells to activate Wnt signaling or JNK activation, and to turn on specific activators of JNK in response to various environmental cues.

L18 ANSWER 11 OF 27 MEDLINE DUPLICATE 9
2000469680 Document Number: 20435343. PubMed ID: 10979959. Homocysteine-responsive ATF3 gene expression in human vascular endothelial cells: activation of c-Jun NH(2)-terminal kinase and promoter response element. Cai Y; **Zhang C**; Nawa T; Aso T; Tanaka M; Oshiro S; Ichijo H; Kitajima S. (Department of Biochemical Genetics, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan.) BLOOD, (2000 Sep 15) 96 (6) 2140-8. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Activating transcription factor (ATF) 3 is a member of ATF/cyclic adenosine monophosphate (cAMP)-responsive element binding protein (ATF/CREB) family of transcription factors and functions as a stress-inducible transcriptional repressor. To understand the stress-induced gene regulation by homocysteine, we investigated activation of the ATF3 gene in human endothelial cells. Homocysteine caused a rapid induction of ATF3 at the transcriptional level. This induction was preceded by a rapid and sustained activation of c-Jun NH(2)-terminal kinase/stress-activated protein kinase (JNK/**SAPK**), and dominant negative mitogen-activated protein kinase kinase 4 and 7 abolished these effects. The effect of homocysteine appeared to be specific, because cysteine or homocystine had no appreciable effect, but it was mimicked by dithiothreitol and beta-mercaptoethanol as well as tunicamycin. The homocysteine effect was not inhibited by an active oxygen scavenger. Deletion analysis of the 5' flanking sequence of the ATF3 gene promoter revealed that one of the major elements responsible for the induction by homocysteine is an ATF/cAMP responsive element (CRE) located at -92 to -85 relative to the transcriptional start site. Gel shift, immunoprecipitation, and cotransfection assays demonstrated that a complex (or complexes) containing ATF2, c-Jun, and ATF3 increased binding to the ATF/CRE site in the homocysteine-treated cells and activated the ATF3 gene expression, while ATF3 appeared to repress its own promoter. These data together suggested a novel pathway by which homocysteine causes the activation of JNK/**SAPK** and subsequent ATF3 expression through its reductive stress. Activation of JNK/**SAPK** and ATF3 expression in response to homocysteine may have a functional role in homocysteinemia-associated endothelial dysfunction.

L18 ANSWER 12 OF 27 MEDLINE DUPLICATE 10
2000441833 Document Number: 20384190. PubMed ID: 10924369. Cloning of DPK, a novel dendritic cell-derived protein kinase activating the ERK1/ERK2 and JNK/**SAPK** pathways. **Zhang W**; Chen T; Wan T; He L; Li N; Yuan Z; Cao X. (Department of Immunology, Second Military Medical University, 800 Xiangyin Road, Shanghai, 200433, People's Republic of China.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Aug 11) 274 (3) 872-9. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Mitogen-activated protein kinase (MAPK) cascades are the major signaling systems transducing extracellular signals into intracellular responses, which mainly include the extracellular signal-regulated kinase (ERK) pathway, the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/**SAPK**) pathway, and the p38 pathway. From dendritic cell cDNA library, we isolated a full-length cDNA encoding a potentially novel

898-residue kinase, which was designated DPK. The protein contained a potential kinase domain at the N-terminal exhibiting homology with MEKK1-, MEKK2-, MEKK3-, MEKK4-, MEKK5-, Tpl-2-, and p21-activated kinases (PAKs), but no GTPase-binding domain which is characteristic of PAKs. Northern blotting analysis showed that DPK was ubiquitously expressed in normal tissues, with abundant expression in kidney, skeletal muscle, heart, and liver. When overexpressed in transfected NIH3T3 cells, it could activate both the ERK1/ERK2 pathway and the **SAPK** pathway in a dose-dependent manner, but not affect the p38 pathway. These findings suggested that DPK might be a novel candidate MAPKKK.

L18 ANSWER 13 OF 27 MEDLINE DUPLICATE 11
2000115960 Document Number: 20115960. PubMed ID: 10650002. Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. Urano F; Wang X; Bertolotti A; **Zhang Y**; Chung P; Harding H P; Ron D. (Skirball Institute of Biomolecular Medicine, Departments of Medicine, Cell Biology and the Kaplan Cancer Center, New York University Medical School, New York, NY 10016, USA.) SCIENCE, (2000 Jan 28) 287 (5453) 664-6. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.
AB Malfolded proteins in the endoplasmic reticulum (ER) induce cellular stress and activate c-Jun amino-terminal kinases (JNKs or **SAPKs**). Mammalian homologs of yeast IRE1, which activate chaperone genes in response to ER stress, also activated JNK, and IRE1alpha-/- fibroblasts were impaired in JNK activation by ER stress. The cytoplasmic part of IRE1 bound TRAF2, an adaptor protein that couples plasma membrane receptors to JNK activation. Dominant-negative TRAF2 inhibited activation of JNK by IRE1. Activation of JNK by endogenous signals initiated in the ER proceeds by a pathway similar to that initiated by cell surface receptors in response to extracellular signals.

L18 ANSWER 14 OF 27 MEDLINE DUPLICATE 12
2000107124 Document Number: 20107124. PubMed ID: 10639328. Phosphorylation of neurofilament heavy chain side-arms by stress activated protein kinase-1b/Jun N-terminal kinase-3. Brownlees J; Yates A; Bajaj N P; Davis D; Anderton B H; Leigh P N; Shaw C E; **Miller C C**. (Department of Neuroscience, The Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.) JOURNAL OF CELL SCIENCE, (2000 Feb) 113 (Pt 3) 401-7. Journal code: 0052457. ISSN: 0021-9533. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Neurofilaments comprise three subunit proteins; neurofilament light, middle and heavy chains (NF-L, NF-M and NF-H). The carboxy-terminal domains of NF-M and NF-H form side-arms that project from the filament and that of NF-H contains multiple repeats of the motif lys-ser-pro, the serines of which are targets for phosphorylation. The level of phosphorylation on the lys-ser-pro repeats varies topographically within the cell; in cell bodies and proximal axons, the side-arms are largely non-phosphorylated whereas in more distal regions of axons, the side-arms are heavily phosphorylated. Here we show that stress activated protein kinase 1b (SAPK1b), a major **SAPK** in neurones will phosphorylate NF-H side-arms both in vitro and in transfected cells. These studies suggest that SAPK1b targets multiple phosphorylation sites within NF-H side-arms. Additionally, we show that glutamate treatment induces activation of SAPK1b in primary cortical neurones and increased phosphorylation of NF-H in cell bodies. This suggests that glutamate causes increased NF-H phosphorylation at least in part by activation of stress activated protein kinases.

L18 ANSWER 15 OF 27 BIOSIS
2000:354250 Document No.: PREV200000354250. Glutamate, neurofilament phosphorylation and neurodegenerative disease. Brownlees, J. (1); Yates, A.; Bajaj, N. P.; Leigh, P. N.; Shaw, C. E.; **Miller, C. C. J.**.

(1) Department of Neuroscience, Institute of Psychiatry, London UK. European Journal of Neuroscience, (2000) Vol. 12, No. Supplement 11, pp. 227. print. Meeting Info.: Meeting of the Federation of European Neuroscience Societies Brighton, UK June 24-28, 2000 ISSN: 0953-816X. Language: English. Summary Language: English.

L18 ANSWER 16 OF 27 MEDLINE DUPLICATE 13
2000102205 Document Number: 20102205. PubMed ID: 10638667. Serine/threonine phosphorylation in cellular signaling for alveolar macrophage phagocytic response to endotoxin. **Zhang P**; Nelson S; Summer W R; Spitzer J A. (Department of Medicine, Section of Pulmonary/Critical Care Medicine, Louisiana State University Medical Center, New Orleans 70112, USA.) SHOCK, (2000 Jan) 13 (1) 34-40. Journal code: 9421564. ISSN: 1073-2322. Pub. country: United States. Language: English.

AB Protein serine/threonine (ser/thr) phosphorylation is an early signaling event in macrophage activation. We investigated the changes in stress-activated protein kinase/c-Jun NH2-terminal kinase (**SAPK**/JNK) activity and effects of phosphatase inhibition on alveolar macrophage (AM) function in rats challenged with intratracheal endotoxin. Animals were sacrificed 90 min post intratracheal lipopolysaccharide (LPS, 100 microg/rat) challenge. AMs were incubated with or without phosphatase inhibitors at 37 degrees C for 30 min. Phagocytosis, CD18 expression, **SAPK**/JNK and phosphatase activities of AMs were determined. LPS challenge activated **SAPK**/JNK activity and enhanced phagocytosis of AMs without altering phosphatase activity in these cells. Inhibition of phosphatase 1 and 2A activity with okadaic acid and calyculin A exerted a bi-phasic effect on AM phagocytic function. Okadaic acid at a concentration of 1 microM increased the mean channel fluorescence intensity (MCF) and the percentage of cells engaged in phagocytosis (percent phagocytosis) in AMs from saline-treated rats. This inhibitor at concentrations of 0.5 and 1 microM enhanced both the MCF and percent phagocytosis of AMs from LPS-challenged rats. Calyculin A at a concentration of 10 nM increased the MCF phagocytosis of AMs from LPS-challenged rats. At higher concentrations (20 and 30 nM), calyculin A showed a suppression on both the MCF and percent phagocytosis of AMs in both saline and LPS groups. AM CD18 expression was not altered following LPS challenge. Phosphatase inhibitors at doses that enhanced AM phagocytosis showed either no effect (okadaic acid) or inhibition (calyculin A) of AM CD18 expression. These results suggest that ser/thr phosphorylation and dephosphorylation participate in mediating the phagocytic response of AMs to LPS.

L18 ANSWER 17 OF 27 MEDLINE DUPLICATE 14
2000013030 Document Number: 20013030. PubMed ID: 10544204. Antigen receptor-induced activation and cytoskeletal rearrangement are impaired in Wiskott-Aldrich syndrome protein-deficient lymphocytes. **Zhang J**; Shehabeldin A; da Cruz L A; Butler J; Somani A K; McGavin M; Kozieradzki I; dos Santos A O; Nagy A; Grinstein S; Penninger J M; Siminovitch K A. (Department of Medicine, University of Toronto, Ontario, Canada M5G 1X5.) JOURNAL OF EXPERIMENTAL MEDICINE, (1999 Nov 1) 190 (9) 1329-42. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The Wiskott-Aldrich syndrome protein (WASp) has been implicated in modulation of lymphocyte activation and cytoskeletal reorganization. To address the mechanisms whereby WASp subserves such functions, we have examined WASp roles in lymphocyte development and activation using mice carrying a WAS null allele (WAS(-)(/)(-)). Enumeration of hemopoietic cells in these animals revealed total numbers of thymocytes, peripheral B and T lymphocytes, and platelets to be significantly diminished relative to wild-type mice. In the thymus, this abnormality was associated with impaired progression from the CD44(-)CD25(+) to the CD44(-)CD25(-) stage of differentiation. WASp-deficient thymocytes and T cells also exhibited

impaired proliferation and interleukin (IL)-2 production in response to T cell antigen receptor (TCR) stimulation, but proliferated normally in response to phorbol ester/ionomycin. This defect in TCR signaling was associated with a reduction in TCR-evoked upregulation of the early activation marker CD69 and in TCR-triggered apoptosis. While induction of TCR-zeta, ZAP70, and total protein tyrosine phosphorylation as well as mitogen-activated protein kinase (MAPK) and stress-activated protein/c-Jun NH(2)-terminal kinase (**SAPK**/JNK) activation appeared normal in TCR-stimulated WAS(-)(/)(-) cells, TCR-evoked increases in intracellular calcium concentration were decreased in WASp-deficient relative to wild-type cells. WAS(-)(/)(-) lymphocytes also manifested a marked reduction in actin polymerization and both antigen receptor capping and endocytosis after TCR stimulation, whereas WAS(-)(/)(-) neutrophils exhibited reduced phagocytic activity. Together, these results provide evidence of roles for WASp in driving lymphocyte development, as well as in the translation of antigen receptor stimulation to proliferative or apoptotic responses, cytokine production, and cytoskeletal rearrangement. The data also reveal a role for WASp in modulating endocytosis and phagocytosis and, accordingly, suggest that the immune deficit conferred by WASp deficiency reflects the disruption of a broad range of cellular behaviors.

L18 ANSWER 18 OF 27 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1999:182167 Document No.: PREV199900182167. Activation of the p38 and JNK/**SAPK** mitogen activated protein kinase pathways during apoptosis mediated by a novel retinoid. **Zhang, Y. (1)**; Hang, Y.; Rishi, A. K.; Sheikh, M. S.; Shroot, B.; Reichert, U.; Dawson, M. I.; Poirer, G.; Fontana, J. A.. (1) Greenebaum Cancer Cent., Univ. Maryland, Baltimore, Md 21201 USA. Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 309. Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research. ISSN: 0197-016X. Language: English.

L18 ANSWER 19 OF 27 MEDLINE DUPLICATE 15
1999159028 Document Number: 99159028. PubMed ID: 10047465. Activation of the p38 and JNK/**SAPK** mitogen-activated protein kinase pathways during apoptosis is mediated by a novel retinoid. **Zhang Y**; Huang Y; Rishi A K; Sheikh M S; Shroot B; Reichert U; Dawson M; Poirer G; Fontana J A. (Department of Medicine and Karmanos Cancer Institute, Wayne State University, Detroit, Michigan, 48201-1932, USA.) EXPERIMENTAL CELL RESEARCH, (1999 Feb 25) 247 (1) 233-40. Journal code: 0373226. ISSN: 0014-4827. Pub. country: United States. Language: English.
AB 6-[3-(1-Adamantyl)]-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437) is a novel retinoid which induces apoptosis in the retinoic acid-resistant HL-60R human leukemia cell line. CD437-mediated poly(ADP-ribose) polymerase (PARP) cleavage and apoptosis of HL-60R cells does not require gene transcription or protein synthesis since it occurs in the presence or absence of either actinomycin D or cycloheximide. Marked activation of both the p38 and the JNK/**SAPK** serine and threonine kinases occurs at 1 h of exposure to CD437 with subsequent PARP cleavage at 2 h and apoptosis noted at 4 to 6 h. CD437 concentrations as little as 10 nM result in p38 activation and apoptosis of HL-60R cells. However, inhibition of p38 activation utilizing the specific inhibitor SB203580 does not block CD437-mediated PARP cleavage or apoptosis. In addition, p38 activation is dependent upon the activation of the caspase system since p38 activation is blocked by the pan ICE inhibitor Z-VAD fmk, which also inhibits CD437-mediated apoptosis and PARP cleavage in these cells. CD437-mediated activation of JNK/**SAPK** is not inhibited by Z-VAD fmk, suggesting that it lies upstream of CD437 activation of caspase activity and subsequent apoptosis. The role of JNK/**SAPK** activation in CD437-mediated apoptosis remains to be defined.

L18 ANSWER 20 OF 27 SCISEARCH COPYRIGHT 2003 ISI (R)
1999:375821 The Genuine Article (R) Number: 194PA. Hypoxic induction of stress kinases (**SAPKS**) and apoptosis.. Zhou L (Reprint); **Dong Z H; Miller C A**. UNIV SO CALIF, SCH MED, LOS ANGELES, CA. JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY (MAY 1999) Vol. 58, No. 5, pp. 199-199. Publisher: AMER ASSN NEUROPATHOLOGISTS INC. 1041 NEW HAMPSHIRE ST, LAWRENCE, KS 66044. ISSN: 0022-3069. Pub. country: USA. Language: English.

L18 ANSWER 21 OF 27 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1998:331419 Document No.: PREV199800331419. Interaction of 14-3-3 proteins with ASK1 kinase that activates **SAPK**/JNK and p38 pathways. **Zhang, L.**; Fu, H.. Emory Univ. Sch. Med., Atlanta, GA 30322 USA. FASEB Journal, (April 24, 1998) Vol. 12, No. 8, pp. A1403. Meeting Info.: Meeting of the American Society for Biochemistry and Molecular Biology Washington, D.C., USA May 16-20, 1998 American Society for Biochemistry and Molecular Biology. ISSN: 0892-6638. Language: English.

L18 ANSWER 22 OF 27 SCISEARCH COPYRIGHT 2003 ISI (R)
1999:984044 The Genuine Article (R) Number: 260QN. Interaction of 14-3-3 proteins with ASK1 kinase that activates **SAPK**/JNK and p38 pathways. **Zhang L (Reprint)**; Fu H. EMORY UNIV, SCH MED, ATLANTA, GA 30322. FASEB JOURNAL (24 APR 1998) Vol. 12, No. 8, Supp. [S], pp. 540-540. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0892-6638. Pub. country: USA. Language: English.

L18 ANSWER 23 OF 27 MEDLINE DUPLICATE 16
1998281477 Document Number: 98281477. PubMed ID: 9620167. Transcriptional induction of cyclooxygenase-2 gene by okadaic acid inhibition of phosphatase activity in human chondrocytes: co-stimulation of AP-1 and CRE nuclear binding proteins. **Miller C; Zhang M**; He Y; Zhao J; Pelletier J P; Martel-Pelletier J; Di Battista J A. (Department of Medicine, University of Montreal, Quebec, Canada.) JOURNAL OF CELLULAR BIOCHEMISTRY, (1998 Jun 15) 69 (4) 392-413. Journal code: 8205768. ISSN: 0730-2312. Pub. country: United States. Language: English.

AB The involvement of serine/threonine protein phosphatases in signaling pathways that control the expression of the cyclooxygenase-2 (COX-2) gene in human chondrocytes was examined. Okadaic acid (OKA), an inhibitor of protein phosphatases 1 (PP-1) and 2A (PP-2A), induced a delayed, time-dependent increase in the rate of COX-2 gene transcription (runoff assay) resulting in increased steady-state mRNA levels and enzyme synthesis. The latter response was dose dependent over a narrow range of 1-30 nmol/L with declining expression and synthesis of COX-2 at higher concentrations due to cell toxicity. The delayed increase in COX-2 mRNA expression was accompanied by the induction of the proto-oncogenes c-jun, junB, junD, and c-fos (but not FosB or Fra-1). Increased phosphorylation of CREB-1/ATF-1 transcription factors was observed beginning at 4 h and reached a zenith at 8 h. Gel-shift analysis confirmed the up-regulation of AP-1 and CRE nuclear binding proteins, though there was little or no OKA-induced nuclear protein binding to SP-1, AP-2, NF-kappaB or NF-IL-6 regulatory elements. OKA-induced nuclear protein binding to 32P-CRE oligonucleotides was abrogated by a pharmacological inhibitor of protein kinase A (PKA), KT-5720; the latter compound also inhibited OKA-induced COX-2 enzyme synthesis. Calphostin C (CalC), an inhibitor of PKC isoenzymes, had little effect in this regard. Inhibition of 12P-CRE binding was also observed in the presence of an antibody to CREB-binding protein (265-kDa CBP), an integrator and coactivator of cAMP-responsive genes. The binding to 32P-CRE was unaffected in the presence of excess radioinert AP-1 and COX-2 NF-IL-6 oligonucleotides, although a COX-2 CRE-oligo competed very efficiently. 32P-AP-1 consensus sequence binding was unaffected by incubation of chondrocytes with KT-5720 or CalC, but was

dramatically diminished by excess radioinert AP-1 and CRE-COX-2 oligos. Supershift analysis in the presence of antibodies to c-Jun, c-Fos, JunD, and JunB suggested that AP-1 complexes were composed of c-Fos, JunB, and possibly c-Jun. OKA has no effect on total cellular PKC activity but caused a delayed time-dependent increase in total PKA activity and synthesis. OKA suppressed the activity of the MAP kinases, ERK1/2 in a time-dependent fashion, suggesting that the Raf-1/MEKK1/MEK1/ERK1,2 cascade was compromised by OKA treatment. By contrast, OKA caused a dramatic increase in **SAPK**/JNK expression and activity, indicative of an activation of MEKK1/JNKK/**SAPK**/JNK pathway. OKA stimulated a dose-dependent activation of CAT activity using transfected promoter-CAT constructs harboring the regulatory elements AP-1 (c-jun promoter) and CRE (CRE-tkCAT). We conclude that in primary phenotypically stable human chondrocytes, COX-2 gene expression may be controlled by critical phosphatases that interact with phosphorylation dependent (e.g., MAP kinases:AP-1, PKA:CREB/ATF) signaling pathways. AP-1 and CREB/ATF families of transcription factors may be important substrates for PP-1/PP-2A in human chondrocytes.

L18 ANSWER 24 OF 27 MEDLINE DUPLICATE 17

1998133664 Document Number: 98133664. PubMed ID: 9475517. Activation of JNK/**SAPK** in primary glial cultures: II. Differential activation of kinase isoforms corresponds to their differential expression. **Zhang P**; Hogan E L; Bhat N R. (Department of Neurology, Medical University of South Carolina, Charleston 29425, USA.) NEUROCHEMICAL RESEARCH, (1998 Feb) 23 (2) 219-25. Journal code: 7613461. ISSN: 0364-3190. Pub. country: United States. Language: English.

AB Recently, we reported on the activation of c-Jun N-terminal kinase (JNK) in primary glial cells noting certain differences in the patterns of kinase activation in astrocytes and oligodendrocytes (Zhang et al., J Neurosci Res 46:114-121;1996). In this extended study, we have examined the activation and expression levels of JNK1 and JNK2 isoforms in different glial cell types including the two in vitro-defined astroglial subtypes (type-1 and type-2), oligodendrocytes and microglia. An in-gel kinase assay of cell extracts and JNK-immunoprecipitates revealed the activation of both JNK1 and JNK2 in type-1 astrocytes in response to TNFalpha, and in microglia, in response to TNFalpha and bacterial lipopolysaccharide. The strong activation of the two JNK isoforms in type-1 astrocytes and microglia contrasted with a predominant activation of JNK1 over JNK2 in type-2 astrocytes and oligodendrocytes, the two glial subtypes sharing a common lineage. Immunoblot and immunocytochemical analyses using isoform-specific antibodies showed a differential expression of the two isoforms in different glial cells thereby accounting for their observed differential activation.

L18 ANSWER 25 OF 27 MEDLINE DUPLICATE 18

1998062169 Document Number: 98062169. PubMed ID: 9400997. ErbB kinases and NDF signaling in human prostate cancer cells. Grasso A W; Wen D; **Miller C M**; Rhim J S; Pretlow T G; Kung H J. (Case Western Reserve University School of Medicine, Department of Molecular Biology and Microbiology, Cleveland, Ohio 44106-4960, USA.) ONCOGENE, (1997 Nov 27) 15 (22) 2705-16. Journal code: 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Prostate carcinoma (PCA) is the most commonly diagnosed malignancy in American men. Our knowledge of PCA growth regulation lags behind that of other cancers, such as breast and colon carcinomas. Among receptor tyrosine kinases, the ErbB family is most frequently implicated in neoplasia. We report here the expression of ErbB family kinases and their ligands in PCA cell lines and a xenograft. While ErbB1/EGFR, ErbB2/NEU, and ErbB3 were always observed in a distinct pattern, ErbB4 was not observed. Interestingly, while TGF-alpha was expressed in the majority of PCA lines, the ligand Neu Differentiation Factor/Heregulin (NDF) was expressed only in an immortalized, non-transformed prostate epithelial

line. Concomitantly, there was a significant difference in biological response to these ligands. NDF inhibited LNCaP growth and induced an epithelial-like morphological change, in contrast to TGF-alpha, which accelerated cell growth. We also performed the first comprehensive analysis of NDF signaling in a prostate line. LNCaP stimulated with NDF demonstrated crosstalk between ErbB3 and ErbB2 which did not involve ErbB1. NDF also turned on several cascades, including those of PI3-K, ERK/MAPK, mHOG/p38 and JNK/**SAPK**, but not those of PLCgamma or the STAT family. This signaling pattern is distinct from that of TGF-alpha. The activation of mHOG by ErbB2 or ErbB3 has not been reported, and may contribute to the unusual phenotype. PI3-K activation is characterized by the formation of a striking 'activation complex' with multiple tyrosine-phosphorylated species, including ErbB3. Our studies provide a framework in which to dissect the growth and differentiation signals of prostate cancer cells.

L18 ANSWER 26 OF 27 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1997:232707 Document No.: PREV199799531910. Selective activation of the JNK/**SAPK** pathway is associated with oncogenic ras-induced phenotypic transition in human lung cancer cells. Xiao, L.; **Zhang, M.**. Univ. Tex. Med. Branch, Galveston, TX 77555 USA. Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 374. Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997 ISSN: 0197-016X. Language: English.

L18 ANSWER 27 OF 27 MEDLINE DUPLICATE 19
97047192 Document Number: 97047192. PubMed ID: 8892112. Activation of C-jun N-terminal kinase/stress-activated protein kinase in primary glial cultures. **Zhang P**; Miller B S; Rosenzweig S A; Bhat N R. (Department of Neurology, Medical University of South Carolina, Charleston 29425, USA.) JOURNAL OF NEUROSCIENCE RESEARCH, (1996 Oct 1) 46 (1) 114-21. Journal code: 7600111. ISSN: 0360-4012. Pub. country: United States. Language: English.

AB Glial cells in the mammalian CNS are subject to environmental stress resulting from a variety of neuro-pathological conditions. In this study, we have examined the activation of a stress signal responsive kinase, i.e., stress-activated protein kinase (**SAPK**) or c-Jun N-terminal kinase (JNK), in primary cultures of rat brain glial cells (i.e., astrocytes and oligodendrocytes) and an oligodendrocyte progenitor cell line, CG4, in response to cytokines and other stress inducers. JNK/**SAPK** activity was measured by an immune complex kinase assay using polyclonal anti-JNK antibodies along with GST c-Jun (1-79) as the substrate. Among the cytokines tested, TNF-alpha had the strongest effect on JNK activation followed by TNF-beta in both the glial cell types while a substantial level of kinase activation was observed in response to IL-1 in astrocytes. JNK activation by TNF-alpha in astrocytes, but not in oligodendrocytes, showed a biphasic response. An in-gel kinase assay of cell extracts and immunoprecipitated JNK confirmed the activation of JNK1 in cells treated with TNF-alpha. JNK was also activated by several other stress-inducing factors including. UV light, heat shock, inhibitors of protein synthesis, and mechanical injury. Incubation of cells with bacterial sphingomyelinase and a cell-permeable ceramide stimulated JNK activity, suggesting that the ceramide pathway may play a role in JNK activation, although the time course of activation did not correspond to that of TNF-alpha. The results are discussed in terms of possible roles of JNK activation in signaling for gliosis in astrocytes and as a protective/toxic response in oligodendrocytes.

=> s l12 and c-Jun amino terminal kinase 3
L19 2 L12 AND C-JUN AMINO TERMINAL KINASE 3

=> dup remove l19
PROCESSING COMPLETED FOR L19
L20 2 DUP REMOVE L19 (0 DUPLICATES REMOVED)

=> d l20 1-2 cbib abs

L20 ANSWER 1 OF 2 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
2002061859 EMBASE Cyclin-dependent kinase 5 prevents neuronal apoptosis by negative regulation of c-Jun N-terminal kinase 3. Li B.-S.; **Zhang L.**; Takahashi S.; Ma W.; Jaffe H.; Kulkarni A.B.; Pant H.C.. H.C. Pant, Laboratory of Neurochemistry, NINDS, NIH, Bethesda, MD 20892-4130, United States. panth@ninds.nih.gov. EMBO Journal 21/3 (324-333) 1 Feb 2002.
Refs: 65.
ISSN: 0261-4189. CODEN: EMJODG. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Cyclin-dependent kinase 5 (cdk5) is a serine/threonine kinase activated by associating with its neuron-specific activators p35 and p39. Analysis of cdk5(-/-) and p35(-/-) mice has demonstrated that both cdk5 and p35 are essential for neuronal migration, axon pathfinding and the laminar configuration of the cerebral cortex, suggesting that the cdk5-p35 complex may play a role in neuron survival. However, the targets of cdk5 that regulate neuron survival are unknown. Here, we show that cdk5 directly phosphorylates c-Jun N-terminal kinase 3 (JNK3) on Thr131 and inhibits its kinase activity, leading to reduced c-Jun phosphorylation. Expression of cdk5 and p35 in HEK293T cells inhibits c-Jun phosphorylation induced by UV irradiation. These effects can be restored by expression of a catalytically inactive mutant form of cdk5. Moreover, cdk5-deficient cultured cortical neurons exhibit increased sensitivity to apoptotic stimuli, as well as elevated JNK3 activity and c. Jun phosphorylation. Taken together, these findings show that cdk5 may exert its role as a key element by negatively regulating the c-Jun N-terminal kinase/stress-activated protein kinase signaling pathway during neuronal apoptosis.

L20 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
1998:177396 Document No.: PREV199800177396. A splicing variant of a death domain protein that is regulated by a mitogen-activated kinase is a substrate for c-Jun N-terminal kinase in the human central nervous system. Yan, Zhang; Zhou, Li; **Miller, Carol A. (1)**. (1) Dep. Pathol., Univ. South. Calif. Sch. Med., 2011 Zonal Ave. MCA 345, Los Angeles, CA 90033 USA. Proceedings of the National Academy of Sciences of the United States of America, (March 3, 1998) Vol. 95, No. 5, pp. 2586-2591. ISSN: 0027-8424. Language: English.

AB The mitogen-activated kinase activating death domain protein (MADD) that is differentially expressed in neoplastic vs. normal cells (DENN) was identified as a substrate for c-Jun N-terminal kinase 3, the first demonstration of such an activity for this stress-activated kinase that is predominantly expressed in the brain. A splice isoform was identified that is a variant of MADD. A protein identical to MADD has been reported to be expressed differentially in neoplastic vs. normal cells and is termed "DENN." We demonstrated differential effects on DENN/MADD in a stressed vs. basal environment. Using in situ hybridization, we localized both the substrate and the kinase to large pyramidal neurons in the human hippocampus. It was interesting that, in four of four patients with neuropathologically confirmed acute hypoxic changes, we detected a unique translocation of DENN/MADD to the nucleolus. These changes were apparent only in neurons sensitive to hypoxia. Moreover, in those cells, translocation of the substrate was accompanied by nuclear translocation of JNK3. These findings place DENN/MADD and JNK in important hypoxia insult-induced intracellular signaling pathways. Our conclusions are important for future studies for understanding these stress-activated mechanisms.

=> s l12 and stroke
L21 1445 L12 AND STROKE

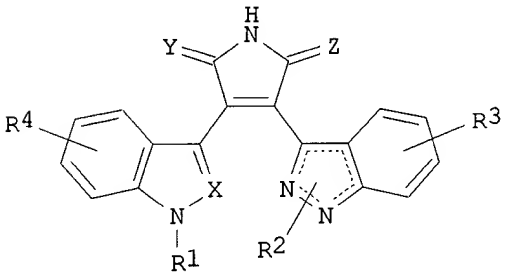
=> s l21 and kinase inhibitor
L22 4 L21 AND KINASE INHIBITOR

=> dup remove l22
PROCESSING COMPLETED FOR L22
L23 4 DUP REMOVE L22 (0 DUPLICATES REMOVED)

=> d l23 1-4 cbib abs

L23 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS
2002:449674 Document No. 137:33321 Preparation of indazolyl-substituted pyrroline compounds as **kinase inhibitors** for treating or ameliorating kinase-mediated disorders. **Zhang, Han-Cheng;** Maryanoff, Bruce; Conway, Bruce; White, Kimberly; Ye, Hong; Hecker, Leonard R.; McComsey, David F. (Ortho-McNeil Pharmaceutical, Inc., USA). PCT Int. Appl. WO 2002046183 A2 20020613, 148 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US47689 20011206. PRIORITY: US 2000-PV254166 20001208.

GI



I

AB Novel indazolyl-substituted pyrroline compds. of formula [I; R1, R2 = H, C1-5 alkyl, C2-8 alkenyl, or C2-8 alkynyl (wherein alkyl, alkenyl and alkynyl are optionally substituted), -C(O)-C1-8 alkyl, -C(O)-aryl-C(O)-O-C1-8 alkyl, -C(O)-O-aryl, -C(O)-NH-C1-8 alkyl, -C(O)-NH-aryl-C(O)-N-[C1-8 alkyl]2, -SO2-C1-8 alkyl, -SO2-aryl, aryl, heteroaryl (wherein aryl and heteroaryl are optionally substituted); X = N, CR5; R3, R4 = H, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C1-8 alkoxy, C(O)H-C(O)-C1-8 alkyl, CO2H, C(O)-O-C1-8 alkyl, CONH2, C(:NH)NH2, C(O)-NH-C1-8 alkyl, C(O)-N(C1-8 alkyl)2, SH, S-C1-8 alkyl, SO2-C1-8 alkyl, SO2NH2, SO2-NH-C1-8 alkyl, SO2-N(C1-8 alkyl)2, N-(un)substituted amino or amino-C1-8 alkyl cyano, halo, (halo)1-3-C1-8 alkyl, (halo)1-3-C1-8 alkoxy, hydroxy, hydroxy-C1-8 alkyl, nitro, aryl, -C1-8 alkylaryl, heteroaryl -C1-8 alkylheteroaryl; Y, Z = O, S, (H,OH), (H,H); with the proviso that one of Y and Z is O and the other is selected from the group consisting of O, S, (H,OH) and (H,H); R5 = hydrogen, halogen, (un)substituted C1-8 alkyl, C2-8 alkenyl, or C2-8 alkynyl] and pharmaceutically acceptable salts thereof are prepd. These compds. are selective inhibitors of kinase or dual inhibitors of at least two kinases selected from protein kinase C,

glycogen synthetase kinase-3, protein kinase C .alpha., protein kinase C .beta.-II, protein kinase C .gamma., glycogen synthetase kinase-3.beta., for treating or ameliorating kinase, and dual-kinase mediated disorders. They are useful for treating or ameliorating a kinase-mediated disorders selected from cardiovascular diseases, diabetes, diabetes-assocd. disorders, inflammatory diseases, immunol. disorders, dermatol. disorders, oncol. disorders and CNS disorders. Thus, 2-[1-(3-pyridyl)indol-3-yl]-2-oxoacetic acid Me ester (700 mg, 2.5 mmol) and 2-[1-(3-dimethylaminopropyl)-1H-indazol-3-yl]acetamide (546 mg, 2.1 mmol) were combined in dry THF (10 mL) under argon and cooled with an ice bath as 1 M potassium t-butoxide in THF (8.4 mL, 8.4 mmol) was added with stirring over a 20 min period. After 1 h, the reaction was quenched in an ice bath by adding 12 N HCl (3.5 mL, 42 mmol) slowly over a 3 min period to give, after purifn. by flash column chromatog., 3-[1-[3-(dimethylamino)propyl]-1H-indazol-3-yl]-4-[1-(3-pyridinyl)-1H-indol-3-yl]-1H-pyrrole-2,5-dione (II). II showed IC50 of 0.007, 0.124, and 0.213 .mu.M against protein kinase C isoforms .beta.-II, .alpha., and .gamma., resp.

L23 ANSWER 2 OF 4 SCISEARCH COPYRIGHT 2003 ISI (R)

2001:369448 The Genuine Article (R) Number: 425AL. Effects of nucleoside transport inhibition on hepatosplanchnic perfusion, oxygen extraction capabilities, and TNF release during acute endotoxic shock. **Zhang H**; De Jongh R; Cherkaoui S; Shahram M; Vray B; Vincent J L (Reprint). Erasme Univ Hosp, Dept Intens Care, Route Lennik 808, B-1070 Brussels, Belgium (Reprint); Erasme Univ Hosp, Dept Intens Care, B-1070 Brussels, Belgium; Univ Toronto, Mt Sinai Hosp, Div Resp Med, Toronto, ON M5G 1X5, Canada; Free Univ Brussels, Fac Med, Dept Immunol, B-1050 Brussels, Belgium. SHOCK (MAY 2001) Vol. 15, No. 5, pp. 378-385. Publisher: BIOMEDICAL PRESS. 1021 15TH ST, BIOTECH PARK STE 9,, AUGUSTA, GA 30901 USA . ISSN: 1073-2322. Pub. country: Belgium; Canada. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB We explored the effects of the nucleoside transport inhibitor draflazine on regional blood flow. O-2 extraction capabilities, and tumor necrosis factor (TNF) release in acute endotoxic shock. Fourteen anesthetized and mechanically ventilated dogs received 2 mg/kg of Escherichia coil endotoxin and were divided into two groups. Seven dogs received 0.1 mg/kg of draflazine 30 min before endotoxin, and 7 dogs served as a control group. Draflazine decreased arterial pressure without influencing cardiac index. Mesenteric and portal blood flow and ileum mucosal perfusion increased, but renal blood flow dramatically decreased. After endotoxemia, the draflazine-treated dogs had a lesser fall in cardiac index, filling pressures, and left ventricular **stroke** work index, and a lesser increase in pulmonary vascular resistance. After fluid resuscitation, they had a consistently lower renal blood flow and ileum mucosal perfusion, but a higher mixed venous and hepatic oxygen saturation and arterial pH than the control group. When cardiac index was reduced by tamponade to study the O-2 extraction capabilities, renal blood flow and ileum mucosal perfusion remained lower in the draflazine group. Draflazine did not influence whole-body O-2 extraction capabilities, but it delayed the occurrence of liver O-2 supply dependency as indicated by a significantly lower liver DO(2)crit (27.7 +/- 3.9 vs. 43.3 +/- 10.8 mL/min) and a higher O(2)ERcrit (62.7 +/- 9.5 vs. 42.5 +/- 7.1%) than controls (both $P < 0.05$). On the other hand, draflazine increased intestinal DO(2)crit (42.4 +/- 15.4 vs. 27.7 +/- 6.5 mL/min, $P < 0.05$) compared to the control group. TNF levels remained higher in the draflazine group than in the control group, particularly 3 and 4 h after endotoxin administration. We conclude that nucleoside transport inhibition with draflazine does not alter global and hepatosplanchnic hemodynamics but may decrease gut mucosal perfusion and renal blood flow. However, this intervention can improve liver O-2 extraction capabilities in acute endotoxic shock.

L23 ANSWER 3 OF 4 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

2001064527 EMBASE Src deficiency or blockade of Src activity in mice provides cerebral protection following **stroke**. Paul R.; **Zhang Z.G.**; Eliceiri B.P.; Jiang Q.; Boccia A.D.; **Zhang R.L.**; Chopp M.; Cheresh D.A.. D.A. Cheresh, Dept. of Immunol. and Vascular Biol., Scripps Research Institute, San Diego, CA, United States. cheresh@scripps.edu. Nature Medicine 7/2 (222-227) 2001.
Refs: 31.
ISSN: 1078-8956. CODEN: NAMEFI. Pub. Country: United States. Language: English. Summary Language: English.

AB Vascular endothelial growth factor (VEGF), an angiogenic factor produced in response to ischemic injury, promotes vascular permeability (VP). Evidence is provided that Src kinase regulates VEGF-mediated VP in the brain following **stroke** and that suppression of Src activity decreases VP thereby minimizing brain injury. Mice lacking pp60(c-src) are resistant to VEGF-induced VP and show decreased infarct volumes after **stroke** whereas mice deficient in pp59(c-fyn) another Src family member, have normal VEGF-mediated VP and infarct size. Systemic application of a Src-inhibitor given up to six hours following **stroke** suppressed VP protecting wild-type mice from ischemia-induced brain damage without influencing VEGF expression. This was associated with reduced edema, improved cerebral perfusion and decreased infarct volume 24 hours after injury as measured by magnetic resonance imaging and histological analysis. Thus, Src represents a key intermediate and novel therapeutic target in the pathophysiology of cerebral ischemia where it appears to regulate neuronal damage by influencing VEGF-mediated VP.

L23 ANSWER 4 OF 4 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

2000136135 EMBASE c-Jun N-terminal kinase (JNK) and JNK interacting protein response in rat brain after transient middle cerebral artery occlusion. Hayashi T.; Sakai K.-I; Sasaki C.; **Zhang W.R.**; Warita H.; Abe K.. T. Hayashi, Department of Neurology, Okayama University Medical School, 2-5-1 Shikata-machi, 700-8558 Okayama, Japan. thayashi@cc.okayama-u.ac.jp. Neuroscience Letters 284/3 (195-199) 28 Apr 2000.
Refs: 18.
ISSN: 0304-3940. CODEN: NELED5.
Publisher Ident.: S 0304-3940(00)01024-7. Pub. Country: Ireland. Language: English. Summary Language: English.

AB c-Jun response is involved in the development of ischemic brain injury, which is activated by c-Jun N-terminal kinase-1 (JNK-1). The activity of JNK-1 is strictly regulated, and only the phosphorylated form of JNK (phospho-JNK) which is translocated to the nucleus has an ability to activate c-Jun response. There is a protein which inhibits JNK-1 activation, and known as JNK interacting protein-1 (JIP-1). In this study, we investigated change in JNK-1, phospho-JNK, and JIP-1 immunoreactivity in rat brain after transient middle cerebral artery (MCA) occlusion. Immunoreactive JNK-1 was scant in the sham-control brain, but it was induced at 1 h after reperfusion, which was slightly increased at 3 h of reperfusion. By contrast, phospho-JNK remained negative till 3 h. At 8 h, JNK-1 and phospho-JNK became distinctly positive, and nuclei as well as cytoplasm were stained. Thereafter, immunoreactivity for JNK-1 and phospho-JNK became furthermore dense, and most neurons revealed positively stained nuclei. Immunoreactivity for JIP-1 remained negative till 8 h of reperfusion, but at 24 and 72 h, cytoplasm of cortical neurons at the MCA boundary area was positively stained. This JIP-1 induction got behind the JNK-1 activation, and therefore, may be a vain effort for neurons to survive. Inhibition of JNK-1 activation might become an innovative means of therapy for **stroke** treatment in the future. Copyright (C) 2000 Elsevier Science Ireland Ltd.

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	147.44	147.65

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-8.46	-8.46

STN INTERNATIONAL LOGOFF AT 15:24:29 ON 02 JAN 2003